ANG1005, A Novel Brain-Penetrant Taxane Derivative, for the Treatment of Recurrent Brain Metastases and Leptomeningeal Carcinomatosis from Breast Cancer

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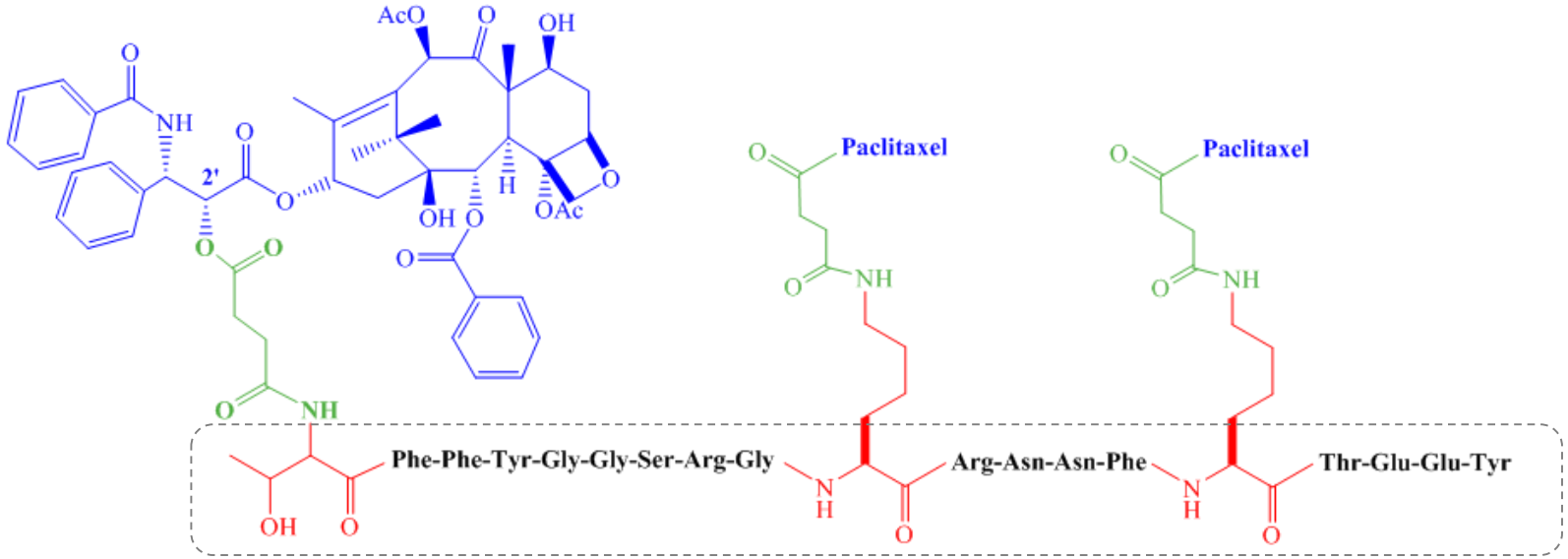
Background: Brain Mets in Breast Cancer

- Up to 30% of the over 200,000 people diagnosed with breast cancer each year in the U.S. will go on to develop brain mets
- Leptomeningeal carcinomatosis (LC): defined as tumor cells in the subarachnoid space/within the CSF
- Brain mets and LC may also be increasing in incidence as systemic therapy improves
- CNS disease as a whole is difficult to treat, with LC being particularly challenging to treat and associated with poor survival outcomes

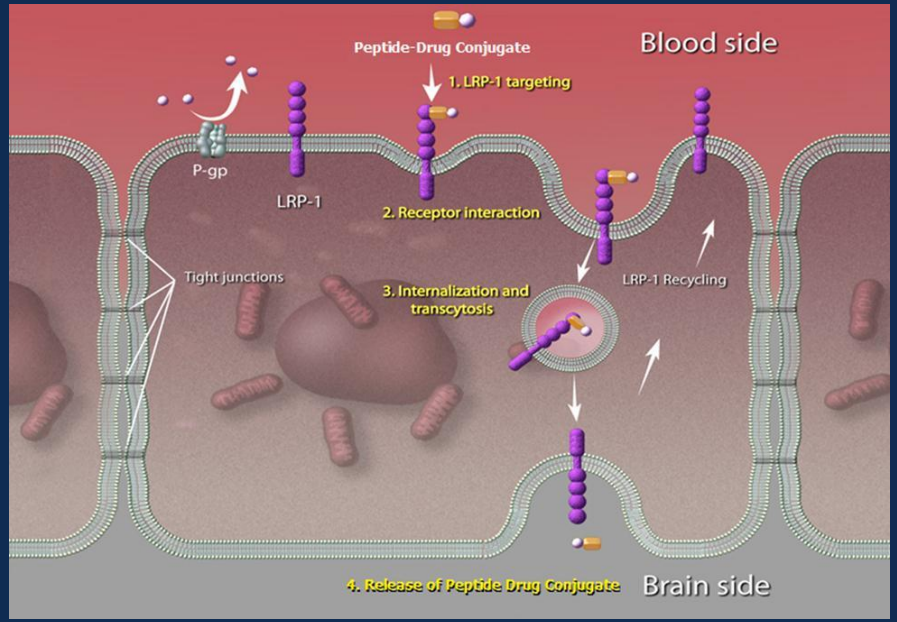
ANG1005 is a peptide drug conjugate: Angiopep-2 + Paclitaxel

ANG1005 Structure

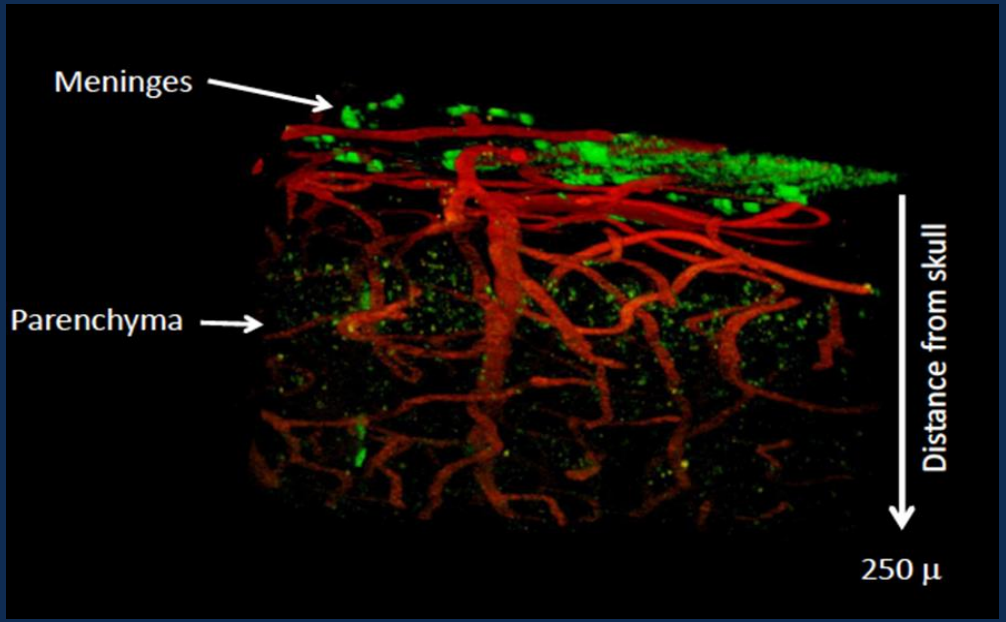


Angiopep-2: ***Binds to LRP -1 receptor***

ANG1005 crosses BBB/BCB via the LRP-1 pathway

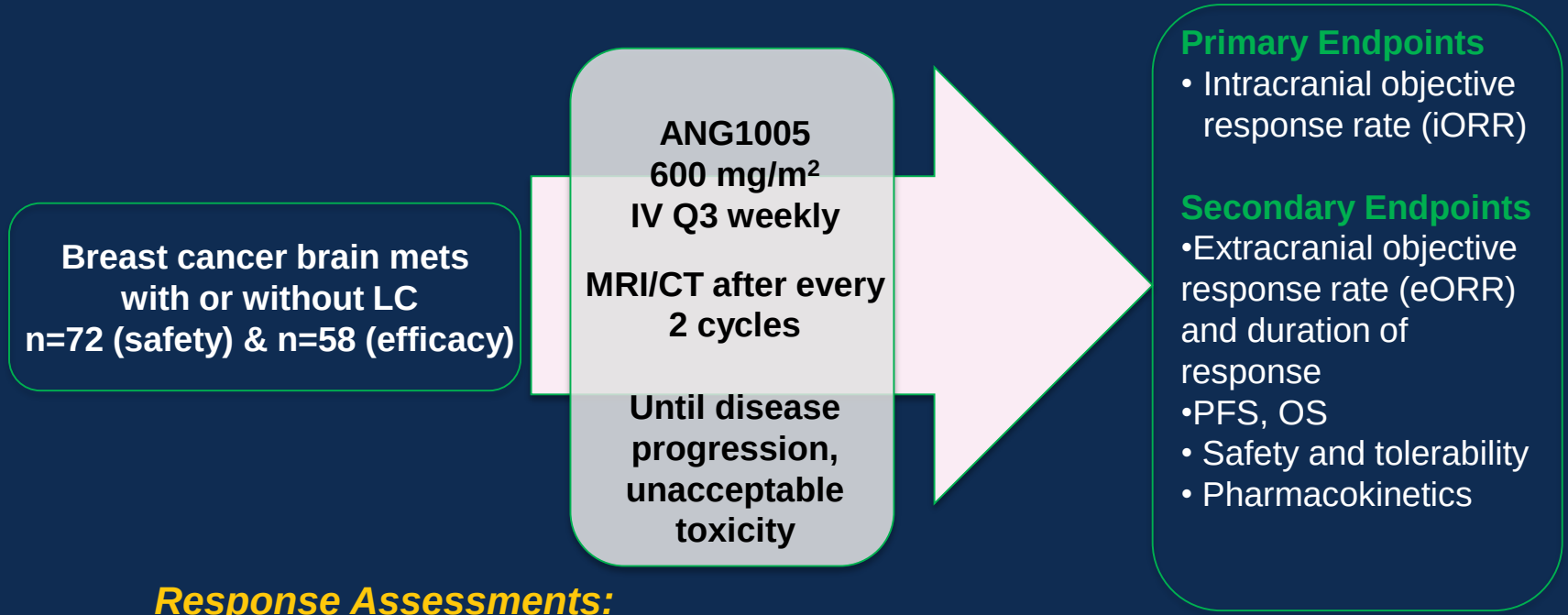


Receptor-Mediated Transcytosis of ANG1005 Across the Endothelial Cells at the Blood-Brain Barrier



Demonstration of Angiopep accumulation in meninges and parenchyma of living mouse brain (intravital imaging 24 hours post IV administration).

Study design: ANG1005-CLN-04 for Recurrent BCBM



Response Assessments:

- *Intracranial tumor responses by modified CNS RECIST v1.1*
- *Extracranial tumor responses by RECIST v1.1*

ANG1005-CLN-04-Baseline Characteristics

	Total n=72
Age, median (range)	47.5 (26-76)
Years since initial diagnosis of breast cancer, median (range)	4.4 (0.8-31)
Years since initial diagnosis of brain mets, median (range)	1.0 (0.05-6.4)
HER2+, n (%)	30 (42%)
HER2-, n (%)	42 (58%)
TNBC, n (%)	19 (26%)
Leptomeningeal carcinomatosis, n (%)	28 (39%)
Prior intracranial surgical resection, n (%)	17 (32%)[a]
Prior intracranial radiotherapy, n (%)	53 (84%)[b]
Prior taxane, n (%)	54 (84%)[c]
Prior anti-HER2 therapy, n (%)	28 (44%)[c]
Prior steroid use, n (%)	23 (33%)[d]

a Incomplete data set, n=54
b Incomplete data set, n=63
c Incomplete data set, n=64
d Incomplete data set, n=69

Safety and tolerability consistent with a taxane profile

Key AEs and Laboratory Abnormalities associated with ANG1005	600 mg/m² (AEs: n=72; Labs: n=70)	
	All grades	Grade ≥ 3
Hematological		
White blood cell count	58 (83%)	44 (63%)
Neutrophil count	49 (70%)	44 (63%)
Lymphocyte count	47 (67%)	30 (43%)
Platelet count	48 (69%)	9 (13%)
Anemia	50 (71%)	8 (11%)
Febrile neutropenia (AE)	11 (16%)	10 (14%)
Neurologic		
Peripheral neuropathy/peripheral sensory neuropathy	21 (29%)	5 (7%)
Gastrointestinal		
Nausea	19 (26%)	3 (4%)
Vomiting	10 (14%)	3 (4%)
General		
Fatigue	30 (42%)	8 (11%)
Mucosal inflammation	11 (15%)	3 (4%)

Data as of April 29, 2016

ANG1005-CLN-04; Best iORR in Per-Protocol Patients

	All Patients	HER2+	HER2-
Sample size, n[a]	58	28	30
PR, n (%)	8 (14%)	4 (14%)	4 (13%)
Confirmed PR, n (%)[b]	3 (5%)	2 (7%)	1 (3%)
SD, n (%)	33 (57%)[c]	19 (68%)[c]	14 (47%)
PD, n (%)	17 (29%)	5 (18%)	12 (40%)
Clinical benefit (SD+PR), (%)	71%	82%	60%

a Based on evaluable patients with clinical or radiological evaluation ≥ 4 weeks from C1D1
b A PR with a ≥28-day confirmation of response
c One patient with SD was pathologically determined to be a complete response (pCR) in an index lesions

Data as of February 29, 2016 as measured by Investigators

ANG1005-CLN-04; Best eORR in Per-Protocol Patients

	All Patients	HER2+	HER2-
Sample size, n[a]	30	13	17
CR, n (%)	1 (3%)	0	1 (6%)
PR, n (%)	2 (7%)	0	2 (12%)
SD, n (%)	24 (80%)	12 (92%)	12 (70%)
PD, n (%)	3 (10%)	1 (8%)	2 (12%)
Clinical benefit (SD+PR), (%)	80%	92%	82%

a Based on evaluable patients with extracranial lesions and evaluation ≥ 4 weeks from C1D1

Data as of February 29, 2016 as measured by Investigators

ANG1005-CLN-04; Best iORR in LC Patients

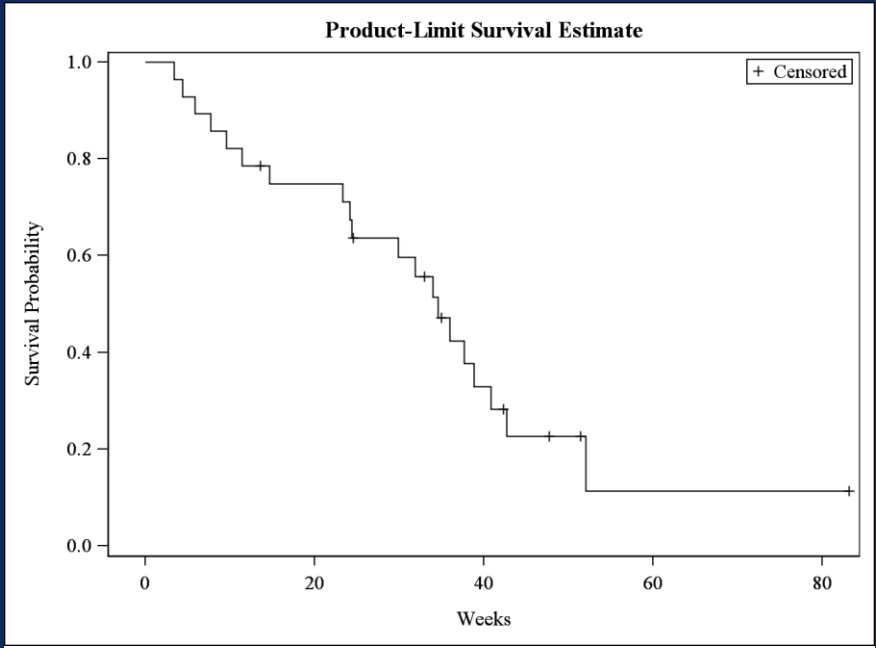
	All LC Patients	HER2+	HER2-
Sample size, n[a]	23	15	8
PR, n (%)	5 (22%)	4 (27%)	1 (13%)
Confirmed PR, n (%)[b]	2 (9%)	2 (13%)	0
SD, n (%)	12 (52%)[c]	8 (53%)[c]	4 (50%)
PD, n (%)	6 (26%)	3 (20%)	3 (37%)
Clinical benefit (SD+PR), (%)	74%	80%	63%

a Based on evaluable patients with clinical or radiological evaluation ≥ 4 weeks from C1D1
b A PR with a ≥28-day confirmation of response
c One patient with SD was pathologically determined to be a complete response (pCR) in an index lesions

Data as of February 29, 2016 as measured by Investigators

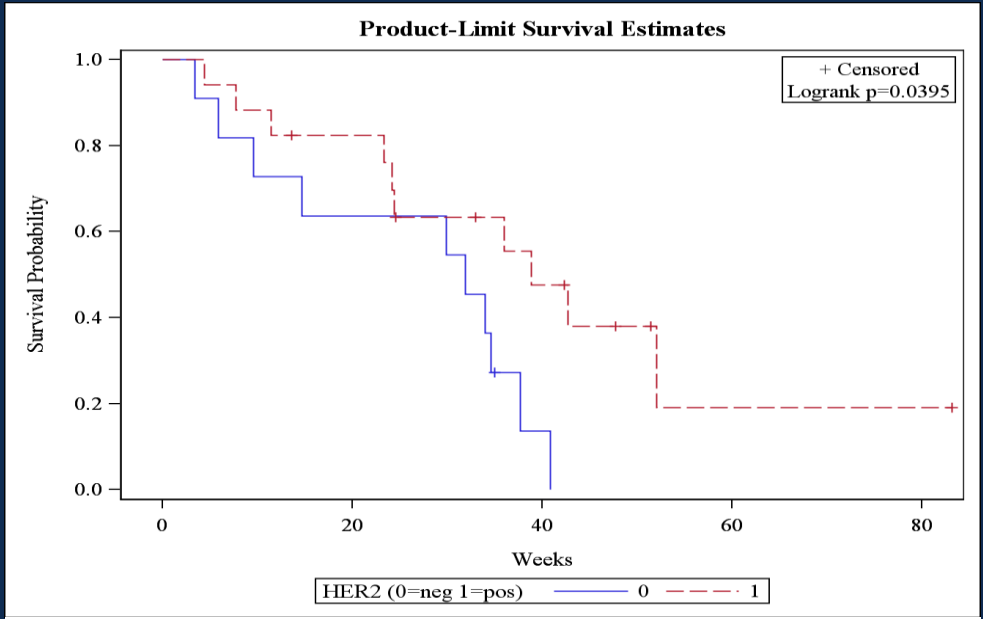
ANG1005-CLN-04 Kaplan-Meier Estimates in LC Patients

All LC Patients



Estimated Median Survival (95% CI): 34.6 weeks/8.0 months (24.1-40.9wks)
OS at 6 months (95% CI): 63.6% (42.9, 78.5)

LC Patients per HER2 Status



HER2+ Median Survival (95% CI): 38.9 weeks/9.0 months (23.3wks-NE)
HER2+ OS at 6 months (95% CI): 63.3% (35.8, 81.6)
HER2- Median Survival (95% CI): 31.9 weeks/7.4 months (5.9-37.7wks)
HER2- OS at 6 months (95% CI): 63.6% (29.7, 84.5)

Data as of April 27, 2016

ANG1005-CLN-04 OS Data in LC patients Compared to Historical Data

	All	HER2+	HER2-
ANG1005-CLN-04 Median OS (months)[a]	8.0	9.0	7.4
De Azevedo *et al*, 2011 Median OS (months)[b]	3.3	No difference	No difference
Abouharb *et al*, 2014 Median OS (months)[b]	3.1	4.4	3.7

a Survival from Cycle 1 Day 1
b Survival from LC diagnosis

Abouharb S. *et al*. Breast Cancer Res Treat. 2014 Aug;146(3):477-86

De Azevedo C. *et al*. J Neurooncol. 2011; 104: 565-572

Conclusions

- Clinical benefit (PR+SD) seen with ANG1005 both intracranially and extracranially in these heavily pretreated recurrent BCBM patients
- Patients with LC had particularly prolonged OS compared to historical controls and many were also seen to have clinical improvement
- The dose and treatment regimen had acceptable tolerability with a safety profile similar to paclitaxel
- A new randomized study in BCBM patients with LC is planned

Acknowledgments

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